PATENT
Attorney Docket No. **OPHD-03282**

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: John A. Kink
Serial No.: 09/095,536 Group No.: 1646
Filed: 06/10/98 Examiner: J. Murphy
Entitled: **Prevention and Treatment of Sepsis**

Appellants Brief

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)

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Dated: January 20, 2005 By: Traci E. Light

Sir or Madam:

Enclosed please find the Appellants Brief and a check for **$500.00** to cover the cost of filing a brief in support of an appeal, relating to the above referenced patent application.

The Commissioner is hereby authorized to charge payment of any fees associated with this communication or credit any overpayment to Deposit Account No. **08-1290**. **An originally executed duplicate of this transmittal is enclosed for this purpose.**

Dated: January 20, 2005

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	John A. Kink		
Serial No.:	09/095,536	Group No.:	1646
Filed:	06/10/98	Examiner:	Murphy, J.
Entitled:	**Prevention And Treatment of Sepsis**		

APPELLANTS BRIEF

APPEAL NO.:

ATTENTION: Board of Patent Appeals and Interferences
Commissioner for Patents and Trademarks
Washington, D.C. 20231

CERTIFICATE OF MAILING UNDER 37 CFR § 1.8(a)

I hereby certify that this paper (along with any referred to as being attached or enclosed) is being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to the: Assistant Commissioner of Patents, Washington, D.C. 20231, on January 20, 2005.

Date: January 20, 2005 By: Traci E. Light

Sir/Madam:

This Brief is in furtherance of the Notice of Appeal mailed on November 23, 2004.

The fees required under § 1.17(c) are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This Brief is transmitted in triplicate. [37 CFR § 1.192(a).]

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This Brief contains these items under the following headings and in the order set forth below [37 CFR § 1.192(c)]:

I. REAL PARTY IN INTEREST

The real party in interest is Promega Corporation, 2800 Woods Hollow Road, Madison WI 53711-5399.

II. RELATED APPEALS AND INTERFERENCES

There are no related applications pending appeal.

III. STATUS OF CLAIMS

The present application (09/095,536), as filed on 06/10/98, contained Claims 1-18. A First Non-Final Office Action (mailed 07/02/99) resulted in a response amending Claim 1 (mailed 10/04/99). A First Final Office Action (mailed 12/22/99) resulted in a response adding Claims 19-23 filed as a CPA (mailed 05/22/00). A Second Non-Final Office Action (mailed 08/29/00) resulted in a response amending Claims 1, 7, and 19 (mailed 11/27/00). A Third Non-Final Office Action (mailed 02/07/01) resulted in a response presenting arguments to rebut rejections based upon anticipation and obviousness (mailed 06/07/00). A Fourth Non-Final Office Action (mailed 08/23/01) resulted in a response amending Claim 7, canceling Claims 13 and 14, and adding new Claims 24-33. A Fifth Non-Final Office Action (mailed 04/09/02) resulted in a response canceling Claims 1-6 and 19-33 (mailed 09/04/02). A Sixth Non-Final Office Action (mailed 11/19/02) resulted in a response adding new Claims 34-48 (mailed 04/21/03). A Seventh Non-Final Office Action (mailed 09/29/03) resulted in a response presenting an argument to rebut a solitary obviousness rejection (mailed 03/29/03). A Second Final Office Action (mailed 06/25/04) rejected Claims 7-12, 15-18, and 34-48 resulting in a Notice of Appeal (mailed 11/23/04).

These claims, as they now stand, are set forth in Appendix A (attached at Tab 1).

IV. STATUS OF AMENDMENTS

All amendments in the case have been entered.

V. SUMMARY OF THE INVENTION

The present invention relates to therapeutics for the prevention and treatment of sepsis, and in particular through the use of antibody therapy. In particular, one example of the present invention demonstrates a novel finding that antibodies against tissue necrosis factor (TNF) in combination with antibodies against interleukin-6 (IL-6) are effective in preventing or treating sepsis.

The present invention also contemplates a method for reducing the symptoms of sepsis. In one embodiment, the present invention contemplates a method of treatment, comprising: (a) providing: i) a mammal having symptoms of sepsis; ii) a therapeutic preparation comprising anti-TNF-α and IL-6 antibodies and (b) administering said preparation to said mammal under conditions wherein said symptoms are reduced. (See Claim 7).

In another embodiment, the present invention contemplates a method of treatment, comprising: (a) providing: i) a mammal having symptoms of sepsis; ii) a therapeutic preparation, *consisting of* anti-TNF-α and anti-IL-6 antibodies, and one or more inactive ingredients; and (b) administering said preparation to said mammal wherein said symptoms are reduced. (See Claim 34).

In another embodiment, the present invention contemplates a method of treatment, comprising: (a) providing: i) a mammal having symptoms of sepsis, ii) a therapeutic preparation, comprising polyclonal anti-TNF-α and polyclonal anti-IL-6 antibodies; and iii) administering said preparation to said mammal wherein said symptoms are reduced. (See Claim 42).

It is preferred that the antibodies not be complement fixing. More specifically, avian antibodies (*e.g.*, chicken antibodies from eggs) are preferred. (See Claims 16-18, 41, and 48). It is also preferred that polyclonal antibodies be employed. (See Claims 15, 40, and 42). It is contemplated that the treatment with such antibodies will have the desired result of reducing mortality rates caused by sepsis.

In various other embodiments, the route of administration may be selected from parenteral, intravenous, and oral. (See Claims 10, 11, 12, 37, 38, 39, 45, 46, and 47).

VI. ISSUES

There are three issues on appeal:

A. Whether The Examiner Has Failed To Make A *Prima Facie* Case Of Obviousness When Combining Brakenhoff *et al.*, United States Patent No. 5,723,120, in view of Doherty *et al. J. Immunol* 149:1666-1670 (1992) and further in view of Emery *et al.*, United States Patent No. 5,420,253 and for the reasons of record set forth in the *Seventh Non-Final Office Action* mailed 09/29/03.

B. Whether The Examiner Has Failed To Consider Rebuttal Evidence Of Non-Obviousness.

C. Whether The Examiner Has Improperly Lumped The Claims Together.

VII. GROUPING OF CLAIMS

Each claim stands alone. Each claim has distinct limitations and must be considered independently.

Independent Claim 7 specifies a method of treatment comprising a mammal having symptoms of sepsis and a therapeutic preparation comprising anti-TNF-α and anti-IL-6 antibodies, wherein the preparation is administered to the mammal. For example, this claim is not limited by the nature of the mammal or the route of administration. Dependent Claim 8 further specifies that the therapeutic preparation further comprises anti-interferon (IFN) antibodies. Dependent Claim 9 further specifies that the mammal is a human. Dependent Claims 10, 11, and 12, respectively, further specify that the antibody may be administered intravenously, orally, or parenterally, respectively. Dependent Claim 15 further specifies that the antibodies are polyclonal antibodies. Dependent Claims 16, 17, and 18, respectively, further specify that the avian antibody is from a chicken, and wherein the antibody is produced in a chicken egg.

Independent Claim 34 specifies a method of treatment comprising a mammal having symptoms of sepsis, a therapeutic preparation consisting of anti-TNF-α and anti-IL-6 antibodies, and one or more inactive ingredients. For example, this claim is not limited by the species, sex, or age of the mammal or the nature of the preparation's inactive ingredients. Dependent Claim 35 further specifies that the inactive ingredient is bovine serum albumin. Dependent Claim 36, further specifies that the mammal is a human. Dependent Claims 37, 38, and 39, respectively, further specify that the antibody may be administered intravenously, orally, or parenterally. Dependent Claim 40 further specifies that the antibodies are

polyclonal antibodies. Dependent Claim 41 further specifies that the polyclonal antibodies are avian antibodies.

Independent Claim 42 specifies a method of treatment comprising a mammal having symptoms of sepsis, a therapeutic preparation comprising polyclonal anti-TNF-α and polyclonal anti-IL-6 antibodies. For example, this claim is not limited by the species, sex, or age of the mammal or the polyclonal antibody source. Dependent Claim 43 further specifies that the therapeutic preparation further comprises anti-IFN antibodies. Dependent Claim 44, further specifies that the mammal is a human. Dependent Claims 45, 46, and 47, respectively, further specify that the antibody may be administered intravenously, orally, or parenterally. Dependent Claim 48 further specifies that the polyclonal antibodies are avian antibodies.

VIII. ARGUMENT

A. Introduction

The Examiner presents Brakenhoff *et al.* as a primary reference. However, Brakenhoff *et al.* teaches IL-6 *receptor* antagonists. As argued below, antibodies directed to IL-6 are distinct from IL-6 receptor antagonists. The Examiner mistates Brakenhoff *et al.* as contemplating a composition comprising antibodies to TNF-α and IL-6. Brakenhoff *et al.* does not teach the use of these antibodies without IL-6 receptor antagonists.

The Examiner admits that Brakenhoff *et al.* "... does not disclose methods of treatment by administration of a composition comprising antibodies to TNF-alpha, IL-6 and IFN-gamma. *Seventh Non-Final Office Action, pg. 3.* Consequently, without further argument, the Board should realize that Claims 8 and 43 are allowable. By ignoring these claim limitations the Examiner has improperly lumped the claims together.

In an attempt to fill this admitted deficiency, the Examiner invokes Doherty *et al.* for disclosing that IFN-gamma is an important mediator of septic shock and that IFN-gamma antibodies are an effective substitute treatment for TNF-alpha antibodies. The Examiner ignores the fact that Doherty *et al.* does not teach any antibody combinations.

The Examiner also admits that "Neither the '120 patent nor Doherty teach antibodies derived from chicken". *Seventh Non-Final Office Action, pg. 4.* In an attempt to fill this deficiency, the Examiner offers Emery *et al.* The Examiner ignores that fact that Emery *et al.* teaches only a standard method to extract and purify avian immunoglobulin. Emery *et al.* is not related to any cytokine antibody or treatment methods for sepsis.

The Applicant provides substantive arguments below: a) showing there is no *prima facie* case for obviousness; and b) rebutting the Examiner's rejection.

B. Claims 7-12, 15-18, And 34-48 Are Not *Prima Facie* Obvious

The Examiner has not properly established the *prima facie* obviousness of the rejected claims. For example, the Examiner makes the conclusory statement:

> The rejection of record set forth that it would have been obvious to one of skill in the art at the time the invention was made to practice a method of treating patients with sepsis with therapeutic compositions comprising anti-TNF, anti-IL-6 and anti-IFN-gamma antibodies that are avian in source.

Second Final Office Action, pg. 3. The Applicant disagrees because the Examiner's statements are: i) unsupported, improper, and contain bald conclusions without a factual basis; and ii) do not meet the proper standards to establish a *prima facie* case of obviousness.

C. The *Prima Facie* Standards Of Obviousness

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference(s) themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference.

Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ.2d 1438 (Fed. Cir. 1991); and *MPEP* § 2142; Establishing A *Prima Facie* Case Of Obviousness. The Examiner is reminded that if ONLY ONE of the above requirements is not met, then a *prima facie* case of obviousness does not exist. The Applicant submits that the Examiner's rejection does not meet any of these criterion.

As a preliminary matter, when dealing with a rejection based upon obviousness it is essential for the Examiner to view the claimed embodiment as a whole:

> [T]he question under 35 U.S.C. § 103 is not whether the differences *themselves* would have been obvious. Consideration of differences, like each of the findings set forth in *Graham*, is but an aid in reaching the ultimate determination of whether the claimed invention *as a whole* would have been obvious.

Stratoflex Inc. v. Aeroquip Corp., 713 F.2d 1530, 1537, 218 USPQ 871 (Fed. Cir. 1983) (emphasis in the original). It is clear to the Applicant that the Examiner has not "stepped back" from the elements to actually "see" the claimed embodiment. Specifically, the Examiner creates the obviousness rejections by "picking and choosing" specific elements among the cited publications and subsequently uses the specification in hindsight.[1] The Federal Circuit has noted that: "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." *In re Fritch,* 972 F.2d 1260, 1266 (Fed. Cir. 1992). The Applicant notes that the Examiner's conclusions allegedly establishing a *prima facie* case of obviousness are not supported by cited reference quotations.

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[1] A practice not permitted under patent law. *See, In re Rouffet, 149 F.3d 1350, 47 USPQ.2d 1453 (Fed. Cir. 1998); and In re Warner,* 379 F.2d 1011, 154 USPQ 173 (CCPA 1967).

D. The References Do Not Teach All The Claim Limitations

The Applicant submits that none of the references teach an anti-TNF-α/anti-IL-6 antibody combination (*i.e.,* for example, avian antibodies). The Examiner's use of Brakenhoff *et al.* for this purpose reveals a misunderstanding of the science in the reference.

1. The Examiner Misunderstands Brakenhoff's Science

The Examiner has taken the position that an antibody is equivalent to a receptor antagonist and misconstrues Brakenhoff *et al.* in an attempt to support this contention (*infra*). The Applicant disagrees from not only a technical science perspective but also upon a patent law basis.

Further, the Examiner has apparently changed position on exactly what the Brakenhoff *et al.* disclosure teaches. Initially, the Examiner admitted that receptor antagonists and antibodies are separate agents:

> The '120 patent further discloses that other agents which may be *combined with IL-6 receptor antagonists* include monoclonal antibodies directed to cytokines involved in the sepsis pathway, such as antibodies directed to IL-6, and antibodies directed to TNF (column 12, lines 44-50). Thus, the '120 patent discloses methods of treating patients with sepsis with therapeutic compositions comprising anti-TNF and anti-IL-6 antibodies.

Sixth Non-Final Office Action, pg. 3 [emphasis added]. The Applicant rebutted the Examiner's conclusion by pointing out that Brakenhoff *et al.* clearly teaches that any monoclonal cytokine antibody composition also contains an IL-6 receptor antagonist, not simply two cytokine antibodies. In maintaining this rejection, the Examiner has ignored the limitations of the Applicant's claims.

In the next office action, the Examiner rephrased Brakenhoff's embodiment from contemplating "... a pharmaceutical composition containing an amount of an IL-6 receptor antagonist effective for treating sepsis ..." (*Sixth Non-Final Office Action. pg 3*) to

contemplating "... a pharmaceutical composition containing an agent which can neutralize IL-6 activity ..." (*Seventh Non-Final Office Action. pg. 3).* This embodiment is not presented in Brakenhoff *et al.* Further, the terms "neutralize", "neutralizing", or "neutralization" occur only in Brakenhoff's Background section. (*infra*; col 2, ln 29-40). The Examiner also recharacterized Brankenhoff's paragraph at col 12 ln 44-50 (*supra*):

> In addition, the '120 patent further discloses that other agents may be *combined with the IL-6 neutralizing agents* include monoclonal antibodies directed to cytokines involved in the sepsis pathway, such as antibodies directed to IL-6, and antibodies directed to TNF (column 12, lines 44-50).

Seventh Non-Final Office Action, pg. 3 [emphasis added]. This is not correct! As the Examiner stated in the *Sixth Non-Final Office Action* (*supra*), col 12 ln 44-50 teaches "IL-6 receptor antagonists" and not the broader term of "IL-6 neutralizing agents". It is fundamental that a receptor antagonist blocks the *receptor*, whereas an antibody to a cytokine neutralizes the cytokine. Consequently, the Examiner has misunderstood basic principles of science.

The Applicant argues that the Examiner has improperly asserted that Brakenhoff *et al.* creates a "design choice" between anti-IL-6 antibodies and anti-IL-6 receptor antagonists:

> ... the '120 patent discloses that other agents may be combined with IL-6 receptor antagonists for the treatment of sepsis, including anti-TNF antibodies (see column 12, lines 44-50). Given the design choice of substituting anti-IL-6 for IL-6 receptor antagonists, this provides the basis for the combination of anti-IL-6 antibodies and anti-TNF antibodies to treat sepsis.

Second Final Office Action, pg. 4. Brakenhoff *et al.* provides no evidence that anti-IL-6 antibodies and anti-IL-6 receptor antagonists are considered equivalent embodiments. Indeed, the only evidence in the reference shows that they are not. Brakenhoff *et al.* specifically teaches that anti-IL-6 receptor antagonists and anti-IL-6 antibodies are not equivalent embodiments by explicitly suggesting their *combination* (rather than substituting one for the other):

> Other agents which may be combined with IL-6 receptor antagonists include ... monoclonal antibodies directed to IL-6 ...

Brakenhoff et al., col 12, ln 44-45. Moreover, Brakenhoff *et al.* admits that IL-6 receptor antagonists were not known in the art at the time the invention was made; a fact the Examiner chose to ignore. The full paragraph cited by the Examiner is presented below:

> Another way to neutralize IL-6 activity is to inhibit the ligand-receptor interaction with specific receptor-antagonists. The feasibility of this general type of approach was recently demonstrated with a natural occurring receptor antagonist to interleukin-1. Hannum. C.H. *et al.*, *Nature* (199) 343:336-340. However, no natural receptor-antagonist has been identified for IL-6 so far. Nor has any hIL-6 variant with antagonistic properties been discovered. This invention uses the information gleaned from the Site I and Site II work with MAbs to construct hIL-6 variants that act as IL-6 receptor antagonists.

Brakenhoff et al., col 2 ln 40-47 (emphasis added). This paragraph, contrary to the Examiner's interpretation, does not teach that one skilled in the art has knowledge of an IL-6 receptor antagonist that neutralizes IL-6 in a manner similar to an IL-6 antibody. In fact, it is an explicit admission that IL-6 receptor antagonists were unknown.

2. Doherty *et al.* Teaches Singular Antibodies

The Examiner admits that Doherty *et al.* is limited to "... administration of antibodies to **either** TNF **or** IFN ...". *Second Final Office Action*, pg. 4 [emphasis added].[2]

Further, Doherty *et al.* only performs protection type experiments. That is to say, antibody is given first, followed by a challenge. The Board is asked to note that Claims 7, 34, and 42 all specify that antibody treatment occurs after the presentation of sepsis symptoms. These claims are supported by the rescue type experiments set forth in the specification. As such, Doherty *et al.* fails to teach all the claim limitations.

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[2] The Examiner is reminded that Doherty *et al.* teaches NO antibody combinations.

3. Emery *et al.* Is Silent On Cytokine Antibodies

The Examiner agrees with Applicant's assertion in the last Office Action response that Emery *et al.* "...lacks any teaching for the administration of antibodies to TNF-G, IL-6 or gamma IFN ..." because the Examiner responds by explaining that "... the '253 patent was cited as disclosing a method for purifying high yields of IgG (IgY) immunoglobulin from chicken egg yolk ...". *Second Final Office Action,* pg. 5.

The Applicant believes, therefore, that because not all the claim limitations are taught by the cited references, the present rejection should be withdrawn.

E. The References Provide No Motivation To Combine

The Examiner's rejection fails upon this basis alone. The Examiner has failed to indicate where in the references cited there is such a suggestion of desirability to combine. The Examiner must provide a *basis* for combining art prior to considering the combination. First, none of the references cited by the Examiner suggest a therapeutic composition comprising the antibodies as combined in the present invention. The law is clear, the mere fact that independent references teach in the same field of endeavor, without a clear suggestion in any reference to combine the collective teachings, is not a legally sufficient basis for *prima facie* obviousness.[3]

Applicant submits that cited references cannot be considered collectively until the Examiner points to some motivation to combine these references. The purpose behind this requirement is to prevent the Examiner from using the invention itself and hindsight

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[3] *Ex parte Dussard,* 7 USPQ2d 1818, 1820 (Bd. Pat. App. & Int., 1988) ("The mere fact that the prior art could be modified in the manner proposed by the Examiner would not have made the modification obvious unless the prior art suggested the desirability of the modification.").

reconstruction to defeat the patentability of the invention. The Federal Circuit, in a recent decision, articulates this position:

> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.

See In re Rouffet et al., 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998). It is readily apparent that the law of *In re Rouffet* requires the Examiner to present soundly reasoned arguments based upon the substance of the cited references.[4] Indeed, the requirement that the Examiner make a showing of a suggestion, teaching or motivation to combine the prior art references is "an essential evidentiary component of an obviousness holding." *C.R. Bard, Inc. v. M3 Sys. Inc.*, 157 F.3d 1340, 1352 (Fed. Cir. 1998). There are three sources for this evidentiary component: the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996). The suggestion most often comes from the teachings of the pertinent references. *In re Rouffet*, 149 F.3d 1350, 1359 (Fed. Cir. 1998). Nonetheless, regardless of the source of the requisite evidence, the Examiner's showing "must be clear and particular, and broad conclusory statements about the teaching of multiple references, standing alone, are not 'evidence'." *In re Dembiczak*, 175 F.3d 994, 1000 (Fed. Cir. 1999). The Examiner has the burden of showing that the cited art is justified by "evidence" which supplies a suggestion, teaching or motivation sufficient to provide one skilled in the art to create the Applicant's invention.

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[4] *Accord Ex parte Clapp*, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (stating that the examiner must present convincing line of reasoning supporting rejection).

Instead, the Examiner presupposes to be "one skilled in the art". The Examiner is reminded that - under the law - an Examiner is NOT one skilled in the art; mere opinion of the Examiner on what one skilled in the art might believe does not count. *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993) ("[T]he examiner's assumptions do not constitute the disclosure of the prior art."). Here, the Examiner has not shown reasons why a skilled artisan would make the combination; the Examiner has merely stated what the Examiner believes. Such unsupported statements are exactly what the *Rouffet* court sought to prevent. The Federal Circuit stated:

> The Board did not ... explain what specific understanding or technological principal within the knowledge of one of ordinary skill in the art would have suggested the combination. *Instead, the Board merely invoked the high level of skill in the art. If such a rote invocation could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technological advance. Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection.* To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

In re Rouffet, 476 USPQ2d at 1458 (emphasis added).

Looking at the cited references themselves, there are no objective teachings that would lead one having ordinary skill in the art to create the Applicant's invention. Indeed, the Examiner points to nothing in the references themselves which teach or suggest the invention. In this manner, the Examiner has not satisfied his burden under the law. *See In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)("[W]hen the PTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears.").

As explained above, Doherty *et al.* does not suggest that antibodies to IFN and TNF should be combined. As such, there is no basis to combine Doherty *et al.* with Brakenhoff *et*

al. or Emery *et al.* Emery *et al.* contains no suggestion that IFN, TNF or IL-6 avian antibodies should be combined to treat sepsis. Similarly, there is no basis to combine Emery *et al.* with either Doherty *et al.* or Brakenhoff *et al.* Brakenhoff *et al.* contains no suggestion that sepsis could be treated with an IFN antibody combination with any other antibody (*i.e.*, for example, avian antibodies). As a result, there is no basis to combine Brakenhoff *et al.* with either Emery *et al.* or Doherty *et al.*

Applicant submits that the Examiner has not provided a sound explanation or evidence for combining these references as required by the law in *In re Rouffett* and *In re Dembiczak.* What the Examiner has provided are unsupported and conclusory legal statements as to why the claimed invention is allegedly obvious over the combination of references.

Because there are no suggestions or motivations within the cited references to support the Examiner's combination, the rejection fails on this prong alone.

F. The References Do Not Teach Reasonable Success

The Examiner has not attempted to establish this prong of *prima facie* obviousness. Applicant submits that the Examiner has deftly ignored this important issue because none of the cited references provide any reasonable expectation of success. This deficiency, alone, must be sufficient to withdraw the present rejection.

This prong of a *prima facie* obviousness rejection is predicated on what the cited reference states, not the Examiner's opinion:

> The expectation of success must come from the prior art and explicitly predict that the process recited in the claims would work.

In re O'Farrell, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988) [emphasis added].

Neither Doherty *et al.*, Brakenhoff *et al.*, or Emery *et al.* explicitly predict that an antibody combination comprising anti-TNF and anti-IL-6 is an effective treatment for sepsis

(*i.e.,* for example, avian antibodies). As explained above, the cited references do not even teach such an antibody combination. Even if the Examiner maintains that Brakenhoff *et al.* discloses an anti-TNF/anti-IL-6 antibody combination (which it does not), clearly the suggested combinations (see col 12 ln 44-50) are mere "invitations to try" and do not teach or guide one having ordinary skill in the art to make a successful choice:

> An invention is 'obvious to try' where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful.

In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673,1681 (Fed. Cir. 1988).

1. Polyclonal Cytokine Antibodies Are Not Taught

Further, the Board is reminded that the production of specific anti-TNF polyclonal antibodies require immunization procedures. TNF immunization is not taught by any of the cited references and, therefore, these references cannot explicitly predict the success of using anti-TNF polyclonal antibodies.

In particular, Brakenhoff *et al.* does not teach or enable polyclonal antibody production (*i.e.,* for example, avian antibodies). Brakenhoff *et al.* teaches only monoclonal antibody production, and not polyclonal antibodies (See Claims 15, 40, and 42):

The production and purification of an IL-6 specific MAb has been described ... *Brakenhoff et al.*, col 13, ln 6-7. By failing to consider the "polyclonal" claim limitation, the Examiner has improperly lumped the claims together.

Importantly, the Examiner's quoted citation (col 12 ln 44-50) contains an incorrect enablement reference citation for TNF-antibodies (Cerami *et al.*, U.S. Pat. No. 4,603,106; col 12 ln 49-50). The '106 patent is silent on both TNF-antibodies and sepsis. Consequently, Cerami *et al.* is not an enabling reference for Brakenhoff *et al.* As the Examiner is aware, all

references cited for obviousness must be enabling.[5] The Applicant concludes, therefore, that Brakenhoff *et al.* is not a proper reference because it is not enabling for TNF-antibodies (*i.e.*, for example, avian TNF-antibodies).

2. Brakenhoff *et al.* Provides Anti-TNF As An Add-On

As explained above, Brakenhoff *et al.* teaches compositions that must contain an IL-6 *receptor* antagonist. The Examiner has repeatedly misrepresented that Brakenhoff *et al.* teaches a composition comprising an anti-TNF antibody and an anti-IL-6 antibody. The Examiner relies exclusively on the text below:

> Other agents which may be combined with IL-6 receptor antagonists include monoclonal antibodies directed to IL-6 or MCSF ... and monoclonal antibodies directed to TNF, see Cerami *et al.* U.S. Pat. No. 4,603,106[6].

Brakenhoff et al. col 12 ln 44-50. This sentence explicitly contemplates: i) IL-6 receptor antagonists combined with IL-6 antibodies; ii) IL-6 receptor antagonists combined with MCSF antibodies; and iii) IL-6 receptor antagonists combined with TNF antibodies. The sentence does not (as the Examiner erroneously argues) contemplate IL-6 antibodies combined with TNF antibodies. The Applicant is confident the Board interprets Brakenhoff *et al.* as contemplating compositions that must include an IL-6 receptor antagonists. The antibodies mentioned above are simple add-ons and only represent an "invitation to experiment" or are "obvious to try". (*supra*) At a minimum, therefore, the Board should realize that, even under the Examiner's improper obviousness combination, Claim 34 is allowable because of the

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[5] In order to render a claimed apparatus or method obvious under Section 103, the prior art must enable one skilled in the art to make and use the apparatus or method. *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989).

[6] Discussed herein as an erroneous reference citation.

closed transition term "consisting of". By failing to consider "consisting of", the Examiner has improperly lumped the claims together.

G. The Applicant's Specification Shows Unexpected Results

Applicant directs the Board's attention to the failure data in the Specification[7] that presents contrary data to that presented in Doherty *et al.* Applicant points to Table 3 in the Specification as rebuttal evidence of non-obviousness where: 1) anti-IFN-γ antibodies administered alone (60 minutes post challenge) failed to save any test animals; and 2) the combination of anti-TNF and anti-IFN-γ antibodies (administered 60 minutes post challenge) failed to save any test animals.

Contrary to Applicant's results in Table 3, shown above, Doherty *et a*l. showed decreased morbidity in test animals upon administration of anti-IFN-γ antibodies alone. Thus, Doherty *et al.* actually suggests the singular administration of anti-IFN-γ antibodies and not the co-administration of anti-IFN-γ antibodies with other anti-cytokine antibodies as disclosed by the present invention. Moreover, contrary to Applicant's results, the Examiner cited Doherty *et a*l. as teaching administration of anti-TNF-α antibodies alone decreases morbidity in test animals.

The Examiner implicitly argued that because a reference individually teaches decreased morbidity in respective test animals, that when they are combined they must also decrease morbidity in test animals because "one therapeutic composition would be expected to give synergistic and more robust effect against septic shock, it would have been easier to administer one composition to a patient than it is to administer three different compositions." *First Final Office Action Mailed July 2, 1999, pg 5.* However, Applicant reminds the Board,

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[7] This failure data was first presented in Applicant's response to the First Non-Final Office Action mailed July 2, 1999.

that the law holds that the Examiner is not skilled in the art, nor, are the Examiner's conclusory assertions evidence of unpatentability (*supra*). Thus, the Examiner's assertion as to the presumptive clinical benefits of co-administering anti-TNF and anti-IFN-γ antibodies to "give synergistic and more robust effect" is without the support required by the law of *In re Rouffet* and is contrary to the Applicant's empirical data.

Indeed, the Applicant empirically showed that the co-administration of anti-TNF and anti-IFN-γ antibodies failed to save any test animals in the test system. The Applicant, therefore, achieved an unexpected result and overcame the morbidity associated with the co-administration of anti-TNF and anti-IFN-γ antibodies by administering the tripartite combination of anti-TNF antibodies, anti-IFN-γ antibodies and anti-IL-6 antibodies, as shown in Table 5.

Applicant submits that the failure data in the instant Specification underscores the non-obviousness of the present invention. Further, Doherty *et al*. reports success using antibody compositions not contemplated in the present invention. It is submitted that the Examiner has failed to properly consider this rebuttal evidence. The Examiner's rejection is thus unwarranted.

IX. CONCLUSION

Appellants submit that, with due consideration to all these factors discussed above, the patentability of Claims 7-12, 15-18, and 34-48 is evident. The standards regarding a *prima facie* case of obviousness are not met. Consequently, the rejection fails.

For the foregoing reasons, it is submitted that the examiner's rejection of Claims 7-12, 15-18, and 34-48 was erroneous, and reversal of this rejection is respectfully requested.

Respectfully submitted,
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Dated: January 20 2005

By: _____
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X. APPENDIX A: CLAIMS INVOLVED IN THE APPEAL

7. A method of treatment, comprising:

a) providing:

i) a mammal having symptoms of sepsis,

ii) a therapeutic preparation, comprising anti-TNF-α and anti-IL-6 antibodies; and

iii) administering said preparation to said mammal wherein said symptoms are reduced.

8. The method of Claim 7, wherein said therapeutic preparation further comprises anti-IFN antibodies.

9. The method of Claim 7, wherein said mammal is a human.

10. The method of Claim 7, wherein said administering is performed intravenously.

11. The method of Claim 7, wherein said administering is performed orally.

12. The method of Claim 7, wherein said administering is performed parenterally.

15. The method of Claim 7, wherein said antibodies are polyclonal antibodies.

16. The method of Claim 15, wherein said polyclonal antibodies are avian antibodies.

17. The method of Claim 16, wherein said avian antibodies are chicken antibodies.

18. The method of Claim 17, wherein said chicken antibodies are derived from chicken eggs.

34. A method of treatment, comprising:

a) providing:

i) a mammal having symptoms of sepsis,

ii) a therapeutic preparation, consisting of anti-TNF-α and anti-IL-6 antibodies, and one or more inactive ingredients; and

iii) administering said preparation to said mammal wherein said symptoms are reduced.

35. The method of Claim 34, wherein said inactive ingredient is bovine serum albumin.

36. The method of Claim 34, wherein said mammal is a human.

37. The method of Claim 34, wherein said administering is performed intravenously.

38. The method of Claim 34, wherein said administering is performed orally.

39. The method of Claim 34, wherein said administering is performed parenterally.

40. The method of Claim 34, wherein said antibodies are polyclonal antibodies.

41. The method of Claim 40, wherein said polyclonal antibodies are avian antibodies.

42. A method of treatment, comprising:

a) providing:

i) a mammal having symptoms of sepsis,

ii) a therapeutic preparation, comprising polyclonal anti-TNF-α and polyclonal anti-IL-6 antibodies; and

iii) administering said preparation to said mammal wherein said symptoms are reduced.

43. The method of Claim 42, wherein said therapeutic preparation further comprises anti-IFN antibodies.

44. The method of Claim 42, wherein said mammal is a human.

45. The method of Claim 42, wherein said administering is performed intravenously.

46. The method of Claim 42, wherein said administering is performed orally.

47. The method of Claim 42, wherein said administering is performed parenterally.

48. The method of Claim 42, wherein said polyclonal antibodies are avian antibodies.